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CORRESPONDENCE



Longer-Term Therapy for Symptoms Attributed to Lyme Disease

TO THE EDITOR: In the placebo-controlled trial by Berende et al. (March 31 issue)¹ involving patients with persistent symptoms attributed to Lyme disease, all the patients received an initial 2-week course of intravenous ceftriaxone. Among the patients who subsequently received placebo, was the 12.6% reduction from baseline in the fatigue score the result of the initial 2-week course of ceftriaxone? The results from other studies that have involved patients with post-treatment symptoms of Lyme disease may help answer this question. In two separate studies, the effect of an intravenous placebo on fatigue was assessed over a 6-month period with the use of an 11-item fatigue-severity scale. In one study, a 9.1% reduction from baseline in the fatigue score was observed in the placebo group,² and in the second study, a 14.5% reduction from baseline was observed in the placebo group.³ Thus, the fact that the magnitude of reduction in fatigue score among the participants who were given placebo in other studies of post-treatment Lyme disease symptoms was similar to that observed in the trial by Berende et al.¹ suggests that the 2-week course of ceftriaxone in this trial probably provided no therapeutic benefit with respect to fatigue.

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Dr. Wormser reports receiving research grants from Immunetics, Institute for Systems Biology, Rarecyte, and Quidel; owning equity in Abbott; having been an expert witness in malpractice cases involving Lyme disease; and being an unpaid board member of the American Lyme Disease Foundation. No other potential conflict of interest relevant to this letter was reported.

1. Berende A, ter Hofstede HJM, Vos FJ, et al. Randomized trial of longer-term therapy for symptoms attributed to Lyme disease. *N Engl J Med* 2016;374:1209-20.

2. Krupp LB, Hyman LG, Grimson R, et al. Study and treatment

of post Lyme disease (STOP-LD): a randomized double masked clinical trial. *Neurology* 2003;60:1923-30.

3. Fallon BA, Keilp JG, Corbera KM, et al. A randomized, placebo-controlled trial of repeated IV antibiotic therapy for Lyme encephalopathy. *Neurology* 2008;70:992-1003.

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TO THE EDITOR: The trial by Berende et al. addresses an often-discussed issue regarding longer treatment duration for persistent symptoms attributed to Lyme disease. Although the inclusion criteria and the design of the study reflect clinical practice and the results are valuable for discouraging unneeded longer-term antibiotic treatment, we would like to highlight an important limitation. The diagnosis of Lyme disease in patients who do not have the classic clinical manifestations is challenging and prone to error.¹ In this trial, a considerable percentage of patients, in particular patients who had nonspecific symp-

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toms and only IgM antibodies, may not have had Lyme disease. The median duration of symptoms was more than 2 years, and therefore positive IgG antibodies, not IgM antibodies, are required to confirm Lyme disease. A total of 22 to 36% of the patients received a diagnosis of Lyme disease on the basis of positive IgM antibodies, and these patients probably did not benefit from any antibiotic treatment because they had received a misdiagnosis. The inclusion of these patients may have blurred a possible difference between the placebo group and the two antibiotic treatment groups, although in our experience as well, longer treatment duration does not have an effect on the severity of symptoms.

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No potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: We agree with Wormser that any effects observed during the follow-up of our patient groups cannot be attributed to ceftriaxone, as was discussed in our article. Our trial was designed to compare longer-term therapy with shorter-term therapy and does not allow for any conclusions to be made on the potential effects of the standardized pretreatment with ceftriaxone in all randomized study groups. As Wormser suggests, the reported changes in outcomes, including fatigue severity, may be ascribed to placebo effects. Responses to placebo are known to contribute to beneficial outcomes in clinical trials, as has been shown for a broad variety of symptoms, including fatigue, and for physiological responses, such as behaviorally conditioned suppression of markers of infection and immunity.¹ Placebo effects are based on the expectations of patients and care professionals regarding the benefits of treatment. These expectations are shaped by a combination of conscious and automatic learning processes, such as conditioning by drug use and patient–physician interactions. Investigators in future trials may disentangle these effects by using more sophisticated

research designs to allow comparisons with the natural course of disease (without any placebo effects) and open-label conditions (to maximize beneficial placebo responses).¹

Erb et al. suggest that patients with *Borrelia burgdorferi* IgM antibodies may not have had Lyme disease. However, IgM antibodies are known to persist for up to 3 years after infection,^{2,3} and false positive IgM immunoblot results occurred in fewer than 10% of healthy controls in a recent study.⁴ Our inclusion criteria aimed at selecting patients who did not have proof of active Lyme disease at baseline but who had been infected by *B. burgdorferi* previously. Patients had to have either documented, proven Lyme disease diagnosed a maximum of 4 months before the onset of symptoms or serologic proof of prior infection, as confirmed by immunoblot assay. Only 25 patients (9%) were included in the trial solely on the basis of positive IgM immunoblot assay results as a marker of prior infection. Among those patients, the physical-component summary score of the RAND-36 Health Status Inventory at the end of therapy was similar to that of patients who were negative for IgM antibodies and did not differ significantly among the study groups. Sensitivity analyses that excluded patients who were positive for IgM antibodies yielded results similar to those of the main analyses. Thus, the assumptions by Erb et al. are unwarranted.

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Since publication of their article, the authors report no further potential conflict of interest.

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